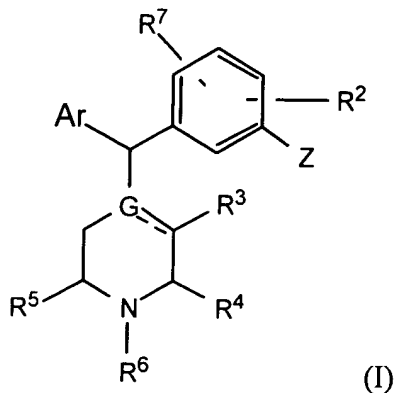


49. The pharmaceutical composition of claim 47, wherein the δ receptor activating agent comprises a diarylmethylpiperazine compound.
50. The pharmaceutical composition of claim 47, wherein the δ receptor activating agent comprises 3290W93.
51. The pharmaceutical composition of claim 47, wherein the δ receptor activating agent comprises BW373U86.
52. The pharmaceutical composition of claim 47, wherein the δ receptor activating agent comprises an agent selected from the group consisting of:

- I. diarylmethylpiperazine compounds;
- II. diarylmethylpiperidine compounds;
- III. deltorphin I; and
- III. deltorphin II.

53. The pharmaceutical composition of claim 47, wherein the δ receptor activating agent comprises an agent selected from the group consisting of:

- I. δ agonist compounds of the formula:



wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent R¹;

Y is selected from the group consisting of:

hydrogen;

halogen;

C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl;

C₁-C₆ haloalkyl;

C₁-C₆ alkoxy;

C₃-C₆ cycloalkoxy;

sulfides of the formula SR⁸ where R⁸ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, arylalkyl having a C₅-C₁₀ aryl moiety and an C₁-C₆ alkyl moiety, or C₅-C₁₀ aryl;

sulfoxides of the formula SOR⁸ where R⁸ is the same as above;

sulfones of the formula SO₂R⁸ where R⁸ is the same as above;

nitrile;

C₁-C₆ acyl;

alkoxycarbonylamino (carbamoyl) of the formula NHCO_2R^8 where R^8 is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $\text{CH}_2\text{NR}^9\text{R}^{10}$ where R^9 and R^{10} may be the same or different, and may be hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_2 - C_6 hydroxyalkyl, C_2 - C_6 methoxyalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_{10} aryl, or R^9 and R^{10} together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $\text{CONR}^9\text{R}^{10}$ where R^9 and R^{10} are the same as above, or C_2 - C_{30} peptide conjugates thereof; and

sulfonamides of the formula $\text{SO}_2\text{NR}^9\text{R}^{10}$ where R^9 and R^{10} are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;

hydroxymethyl, and esters thereof; and

amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

R^1 is hydrogen, halogen, or C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_1 - C_4 alkynyl;

R^2 is hydrogen, halogen, or C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_1 - C_4 alkynyl;

R^3 , R^4 and R^5 may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of R^3 , R^4 or R^5 is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of R^3 , R^4 and R^5 together may form a bridge of 1 to 3 carbon atoms;

R^6 is selected from the group consisting of:

hydrogen;

C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl;

C₃-C₆ cycloalkyl;

arylalkyl having C₅-C₁₀ aryl and C₁-C₆ alkyl moieties;

alkoxyalkyl having C₁-C₄ alkoxy and C₁-C₄ alkyl moieties;

C₂-C₄ cyanoalkyl;

C₂-C₄ hydroxyalkyl;

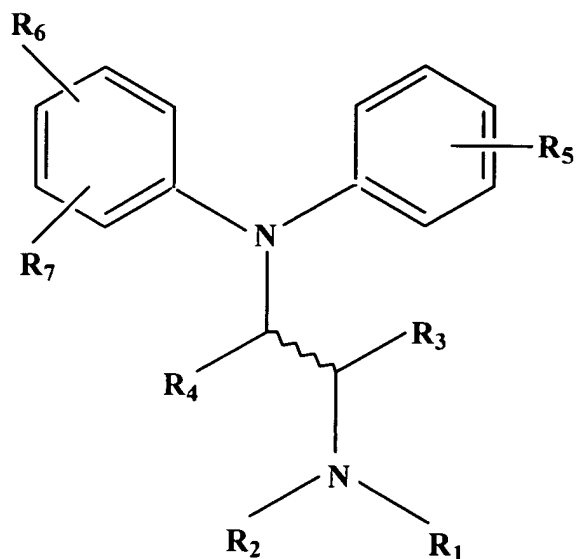
aminocarbonylalkyl having a C₁-C₄ alkyl moiety; and

$R^{12}COR^{13}$, where R^{12} is C₁-C₄ alkylene, and R^{13} is C₁-C₄ alkyl or C₁-C₄ alkoxy; and

R^7 is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof;

II. delta agonist compounds of the formula:



in which,

R₁ and R₂, which can be the same or different, are each hydrogen, linear or branched C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkenyl, C₄₋₆ cycloalkylalkyl, C₃₋₆ alkenyl, C₃₋₅ alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a C₃₋₇ alkyl ring which may be interrupted by oxygen.

R₃ and R₄, which can be the same or different, are each hydrogen, linear or branched C₁₋₆ alkyl, or R₄ is oxygen forming with the carbon atom to which is attached a C=O group;

R₅ is hydrogen, hydroxy, C₁₋₃ alkoxy, thiol or alkylthio;

R₆ is phenyl, halogen, NH₂ or a para or meta -C(Z)-R₈ group, in which Z is oxygen or sulphur;

R₈ is C₁₋₈-alkyl, C₁₋₈-alkoxy or NR₉R₁₀, wherein R₉ and R₁₀, which may be the same or different, are hydrogen, straight or branched C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₄₋₆ cycloalkylalkyl, C₃₋₆ alkenyl, aryl or aralkyl,

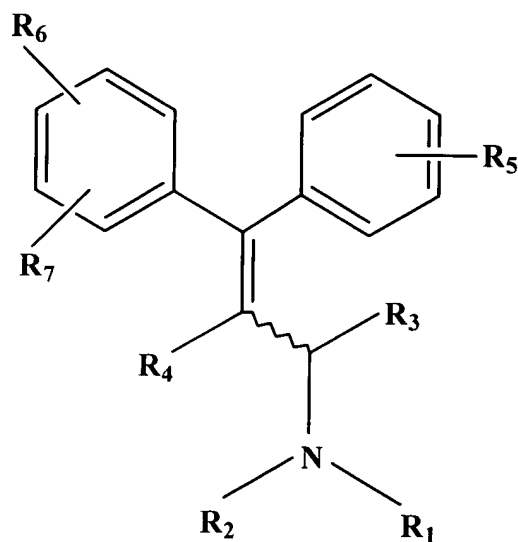
or R₆ is a para or meta -N-C(Z)-R₁₂ group



in which R_{11} and R_{12} which may be the same or different are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl, aralkyl or an optionally substituted heterocyclic ring, and Z is as defined above; and,

R_7 is hydrogen, straight or branched C_{1-8} alkyl or halogen; and

III. delta agonist compounds of the formula:



in which,

R_1 and R_2 , which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, C_{3-5} alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a C_{3-7} alkyl ring which may be interrupted by oxygen.

R_3 and R_4 , which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl;

R_5 is hydroxy, C_{1-6} alkoxy, thiol or alkylthio;

R_6 is a $-C(Z)-R_8$ group, in which Z is oxygen or sulphur, R_8 is C_{1-8} -alkyl, C_{1-8} -alkoxy or NR_9R_{10} , wherein R_9 and R_{10} , which may be the same or different, are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl or aralkyl,

or R₆ is a $\begin{array}{c} R_{11} \\ | \\ -N-C(Z)-R_{12} \end{array}$ group

in which R₁₁ and R₁₂ have the same meaning as R₉ and R₁₀ or together form an optionally substituted heterocyclic ring and Z is as defined above, and R₇ is hydrogen, straight or branched C₁₋₈ alkyl or halogen.

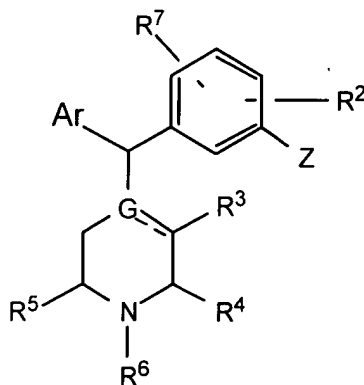
54. The pharmaceutical composition of claim 47, in a form suitable for injectable or spinal administration.

55. A pharmaceutical composition comprising:

(a) an effective amount of a bioactive compound mediating respiratory depression; and

(b) an effective amount of a non-polypeptide δ receptor activating agent effective for combating said respiratory depression.

56. A pharmaceutical composition comprising an effective amount of a bioactive composition mediating respiratory depression, and an effective amount of a compound for reducing, treating or preventing respiratory depression, of the formula:



(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent R¹;

Y is selected from the group consisting of:

hydrogen;

halogen;

C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl;

C₁-C₆ haloalkyl;

C₁-C₆ alkoxy;

C₃-C₆ cycloalkoxy;

sulfides of the formula SR⁸ where R⁸ is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, arylalkyl having a C₅-C₁₀ aryl moiety and an C₁-C₆ alkyl moiety, or C₅-C₁₀ aryl;

sulfoxides of the formula SOR⁸ where R⁸ is the same as above;

sulfones of the formula SO₂R⁸ where R⁸ is the same as above;

nitrile;

C₁-C₆ acyl;

alkoxycarbonylamino (carbamoyl) of the formula NHCO₂R⁸ where R⁸ is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $\text{CH}_2\text{NR}^9\text{R}^{10}$ where R^9 and R^{10} may be the same or different, and may be hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_2\text{-C}_6$ hydroxyalkyl, $\text{C}_2\text{-C}_6$ methoxyalkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, or $\text{C}_5\text{-C}_{10}$ aryl, or R^9 and R^{10} together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $\text{CONR}^9\text{R}^{10}$ where R^9 and R^{10} are the same as above, or $\text{C}_2\text{-C}_{30}$ peptide conjugates thereof; and

sulfonamides of the formula $\text{SO}_2\text{NR}^9\text{R}^{10}$ where R^9 and R^{10} are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;

hydroxymethyl, and esters thereof; and

amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

R^1 is hydrogen, halogen, or $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_1\text{-C}_4$ alkynyl;

R^2 is hydrogen, halogen, or $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_1\text{-C}_4$ alkynyl;

R^3 , R^4 and R^5 may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of R^3 , R^4 or R^5 is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of R^3 , R^4 and R^5 together may form a bridge of 1 to 3 carbon atoms;

R^6 is selected from the group consisting of:

hydrogen;

C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl;

C₃-C₆ cycloalkyl;

arylalkyl having C₅-C₁₀ aryl and C₁-C₆ alkyl moieties;

alkoxyalkyl having C₁-C₄ alkoxy and C₁-C₄ alkyl moieties;

C₂-C₄ cyanoalkyl;

C₂-C₄ hydroxyalkyl;

aminocarbonylalkyl having a C₁-C₄ alkyl moiety; and

$R^{12}COR^{13}$, where R^{12} is C₁-C₄ alkylene, and R^{13} is C₁-C₄ alkyl or C₁-C₄ alkoxy; and

R^7 is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof.

57. The pharmaceutical composition according to claim 56, wherein Ar is a 6-member carbocyclic aromatic (benzene) ring and R^1 is hydrogen.

58. The pharmaceutical composition according to claim 56, wherein Y is a carboxamide of the formula $CONR^9R^{10}$.

59. The pharmaceutical composition according to claim 56, wherein R^9 and R^{10} together form a ring of five or six atoms, thereby forming a pyrrolidinyl or piperidino ring.

60. The pharmaceutical composition according to claim 56, wherein R^9 and R^{10} are the same or different and are each independently selected from hydrogen, C_1 alkyl and C_2 alkyl.

61. The pharmaceutical composition according to claim 56, wherein Y is hydrogen.

62. The pharmaceutical composition according to claim 56, wherein Y is a sulfone of the formula SO_2R^8 and R^8 is C_1 - C_6 alkyl.

63. The pharmaceutical composition according to claim 56, wherein G is N, R^7 and R^2 are each hydrogen, and Z is hydroxyl.

64. The pharmaceutical composition according to claim 56, wherein R^6 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl and C_2 - C_6 alkynyl.

65. The pharmaceutical composition according to claim 56, wherein R^3 , R^4 and R^5 are hydrogen or methyl, where the total number of methyl groups is one or two.

66. The pharmaceutical composition according to claim 56, wherein R^3 and R^5 are both methyl, and R^4 is hydrogen.

67. The pharmaceutical composition according to claim 47, wherein the δ receptor activating agent comprises a compound selected from the group consisting of:

(-)-4-((αR)- α -((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

(-)-4-((αR)- α -((2R,5R)-2,5-dimethyl-4-propyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

4-((αR)- α -(2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzylbenzamide;

(±)-3-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

N,N-diethyl-4-((αR)-3-hydroxy-α-((2R,5R)-2,5-dimethyl-1-piperazinyl)benzyl)benzamide;

4-((αR)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-methylbenzamide;

3-((αR)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

(±)-N,N-diethyl-4-((αR*)-3-hydroxy-α-((2R*,5S*)-2,4,5-trimethyl-1-piperazinyl)benzyl)benzamide;

(+)-4-((αS)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

3-((αR)-4-(piperidinocarbonyl)-α-((2S,5S)-2,4,5-trimethyl-1-piperazinyl)benzyl)phenol;

3-((αR)-4-(1-pyrrolidinylcarbonyl)-α-((2S,5S)-2,4,5-trimethyl-1-piperazinyl)benzyl)phenol;

(±)-3-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-4-(methylsulfonyl)benzyl)phenol;

(±)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

(+)-4-((αR)-α-((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide; or

(-)-4-((αR)-α-((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

(±)-3-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

(±)-4-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

(±)-4-((αR*)-α-((2R*,5S*)-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

(±)-cis-4-(α-(4-allyl-3,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

cis-4-(α-(3,5-dimethyl-4-(methylallyl)-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

and pharmaceutically acceptable salts thereof.

68. The pharmaceutical composition of claim 47, wherein the δ receptor activating agent comprises

(-)-4-((αR)-α-((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide or a pharmaceutically acceptable salt thereof.

69. The pharmaceutical composition of claim 47, wherein the bioactive compound comprises an opiate compound.

70. The pharmaceutical composition of claim 47, wherein the bioactive compound comprises an opiate analgesic compound.

71. The pharmaceutical composition of claim 47, wherein the bioactive compound comprises a μ opiate compound.

72. The pharmaceutical composition of claim 47, wherein the bioactive compound comprises at least one active ingredient selected from the group consisting of alcohol, aldesleukin, alfentanil, bremazocine, buprenorphine, butorphanol, chlorpromazine, clozapine, codeine, dantrolene, diazepam, dihydrocodeine, etorphine, fentanyl, flurazepam, heroin, hydrocodone, hydromorphone, ketamine, larazepam, levallorphen, levorphanol, meperidine, methadone, methohexital, mitomycin, morphine, nalbuphine, opium, oxazepam, oxycodone, oxymorphone, pentazocine, phenobarbital, porfimer, propoxyphene, resperidone, sufentanil, temazepam, thiopental, thiorzadine, tramadol, trimethaphan, and zolpidem.

73. A pharmaceutical composition comprising: